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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,609	02/21/2002	Stefan Kochanek	50125/020002	7269

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,609	KOCHANEK ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *7,8,11-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,10,21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-25 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/10/05 has been entered.

Applicant's traversal and the amendment to the claims filed on 2/10/05 is acknowledged and considered.

Election/Restrictions

An iris pigment epithelial cell in claim 2 and claims 7, 8, and 11-20 and an anti-angiogenetic factor, anti-oxidative factor, lysosomal factor, vasodilating factor in claim 3 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and GDNF, NGF, BDNF, CNTF, bFGF and neurotrophin 3, 4-5 in claim 3 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/20/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 9, 10, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 10, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: delivering an adenoviral vector to a pigment epithelial cell, wherein the adenoviral vector comprises no adenoviral coding DNA sequence. The claims are incomplete for missing an active step for producing the pigment epithelial cell.

Claim 9 is also rejected under 112 second paragraph because of the term "adenoviral vector with large DNA capacity" on line 3. It is undefined if the term is the same as an adenoviral vector comprising no adenoviral coding DNA sequence. Applicants amended the product claim (instant claim 1) to recite a pigment epithelial cell comprising an adenoviral vector comprising no adenoviral coding DNA sequence and did not amend claim 9 to reflect the amendment to the product claim.

Claim Rejections - 35 USC § 103

The e following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The intended use of the genetically modified pigment cell of the eye (e.g., in a fixed assemblage of cells) in the instant claim 6 does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

The intended use of the genetically modified pigment cell of the eye (e.g., medicament or diagnostic aid) in the instant claim 21 does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

The intended use of the genetically modified pigment cell of the eye (e.g., where the cell has been cultivated in the presence of a feeder layer or in serum free-medium) in the instant claims 23 and 24, respectively, does not have patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and the prior art.

Claims 1, 2, 4-6, 9, and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999 (English translation of article in German provided by applicants on a PTO-1449, pages 1-15).

Reichel teaches that after subretinal injection of adenovirus, a very efficient transduction of the RPE can be recognized and gene expression is observed in RPE (page 7). Reichel teaches that a cDNA controlled by CMV promoter was administered to RPE using an adenovirus (pages 11 and 14-15). The RPE cell would read on the limitation in instant claim 5 because one of ordinary skill in the art would consider any endogenous protein (e.g., RPE65) produced by the cell to be therapeutic since the protein is required by the cell to function. The RPE cell would read on the limitation in instant claim 22 because one of ordinary skill in the art would understand that in order to produce an endogenous protein an endogenous DNA sequence would be transcribed into a RNA sequence than translated into a protein. Reichel teaches a retina comprising encapsidated adenovirus mini chromosomes (EAMs), wherein the adenovirus has a gene regulated by a promoter (pages 3, 7-8, and 10). The adenovirus lacks all viral genes and the immunogenicity of the vector is reduced (page 8). In addition, the EAMs can be purified to high titers and have a packaging size of 36kb (page 8). However, Reichel does not specifically teach

a retinal pigment epithelial (RPE) cell comprising an adenovirus comprising a nucleic acid operatively linked to a promoter, wherein the adenovirus comprises no adenoviral coding sequences (gutted adenoviral vector) and method of producing the RPE cell.

Accordingly, in view of the prior art represented by Reichel, one of ordinary skill in the art would have had sufficient motivation to produce RPE cells comprising an adenovirus comprising a nucleic acid operatively linked to a promoter, in particular recombinant adenovirus comprising no adenoviral coding DNA sequences, with a reasonable expectation of success.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, namely to produce a RPE cell comprising EAMs comprising a nucleic acid operatively linked to a promoter. One of ordinary skill in the art would have been motivated to produce a RPE cell comprising said EAM because Reichel teaches that EAMs are an improvement over adenoviral vectors having adenoviral coding DNA sequence because EAMs have reduced immunogenicity compared to an adenovirus having adenoviral coding DNA sequences; EAMS also can deliver larger nucleic acids compared to an adenovirus having adenoviral coding DNA sequences; and EAMs can be used to deliver the nucleic acid to the cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, namely to use EAMs in a method for producing a RPE cell comprising EAMs comprising a nucleic acid operatively linked to a promoter. One of ordinary skill in the art would have been motivated to use EAMs to produce said RPE cell because Reichel teaches that EAMs are an improvement over adenoviral vectors with adenoviral coding DNA sequences and EAMs can be used to deliver the nucleic acid to the cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1, 2, 4-6, 9, and 21-24 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Kovesdi (US 2003/0045498).

Reichel teaches that RPE are available for ex vivo gene transfer (page 4). However, Reichel does not specifically teach genetically modified retinal pigment epithelial cell (RPE) of the eye with an adenoviral vector comprising a nucleic acid encoding PEDF operatively linked to a promoter.

However, at the time the invention was made, Kovesdi teaches administering an adenoviral vector comprising a nucleic acid sequence encoding a pigment epithelium-derived factor (PEDF) to retinal pigment epithelial cells (abstract, pages 2, 3, 4, 6, 15, and 16). Kovesdi teaches that the adenoviral vector is deficient in genes essential for viral replication such that the vector can accept large inserts of exogenous DNA (pages 4-5). Kovesdi teaches that any promoter can be used in the vector, e.g., constitutive, regulatable, tissue-specific (pages 6-7). Kovesdi teaches a pharmaceutical composition comprising the vector and using the vector to study treatment of ocular disorders (pages 12 and 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Kovesdi to produce a

genetically modified pigment epithelial cell comprising an adenoviral vector comprising a nucleic acid encoding PEDF operatively linked to a promoter, wherein the vector comprises no adenoviral coding DNA sequence. One of ordinary skill in the art would have been motivated to produce the cell to study the treatment of ocular disorders by expressing PEDF. In addition, one ordinary skill in the art would have been motivated to use EAM instead of the adenoviral vector taught by Kovesdi for producing the cell because EAM have reduced immunogenicity compared to adenoviral vector having adenoviral DNA coding sequence because it does not contain adenoviral coding DNA sequences and would result in an increase in PEDF expression in the cell because the immune response would not interfere with EAM before EAM transfects the cell and expresses the PEDF.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/10/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Tezel et al., (Exp. Eye Res. (1998) 66, 807-815).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically modified retinal pigment epithelial cell (RPE) of the eye in serum-free media.

However, at the time the invention was made, Tezel teaches that serum-free media can be used for culturing RPE cells (page 807). Tezel further teaches culturing the cells onto tissue-culture plastic pre-coated with bovine corneal endothelial extracellular matrix (page 807). Tezel teaches, "The presence or absence of serum-derived hormones, cytokines, carrier proteins, cell attachment factors and cell spreading factors can have a profound effect on the behavior of RPE cells in tissue culture and may mask the specific effects of a particular exogenous cytokine(s) on RPE. For these reasons, several researchers have cultured RPE with reduced or not serum supplementation (page 807)." Tezel teaches, "This is particularly important for RPE, because RPE cells exhibit phenotypic heterogeneity (page 812)."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Tezel to culture genetically modified retinal pigment epithelial cells in serum-free media. One of ordinary skill in the art would have been motivated to culture the RPE cells in serum-free media because Tezel teaches that culturing RPE cells in serum-free medium avoids the effect of hormone, cytokines, carrier proteins, cell attachment factors and cell spreading factors on the behavior of RPE cells in tissue culture.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/10/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Funk et al., (US 6,667,176) and Williams et al., (Nature, 1988, 336:684-7).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically modified retinal pigment epithelial (RPE) cell of the eye in the presence of a feeder layer.

However, at the time the invention was made, Williams teaches that maintenance of stem-cell phenotype in vitro requires the presence of a feeder layer (page 684).

In addition, at the time the invention was made, Funk teaches that RPE cells are progenitor cells (column 17, lines 34-57).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Williams and Funk to culture genetically modified retinal pigment epithelial cells in the presence of a feeder layer. One of ordinary skill in the art would have been motivated to culture the RPE cells in the presence of a feeder layer because Williams teaches that culturing stem cells in the presence of a feeder layer maintains stem-cell phenotype *in vitro* and Funk teaches that RPE cells are progenitor cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/10/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Claims 1 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reichel et al. (Ophtalmologe, 96:570-577, 1999) as applied to claims 1, 2, 4-6, 9, and 21-24 above, and further in view of Funk et al., (US 6,667,176), Williams et al., (Nature, 1988, 336:684-7) and Tezei et al., (Exp. Eye Res. (1998) 66, 807-815).

Reichel teaches that RPE are available for ex vivo gene transfer because of the possibility of culturing (page 4). However, Reichel does not specifically teach culturing the genetically modified retinal pigment epithelial (RPE) cell of the eye in a serum-free medium and in the presence of a feeder layer.

However, at the time the invention was made, Williams teaches that maintenance of stem-cell phenotype in vitro requires the presence of a feeder layer (page 684). In addition, Funk teaches that RPE cells are progenitor cells (column 17, lines 34-57).

Furthermore, at the time the invention was made, Tezel teaches that serum-free media can be used for culturing RPE cells (page 807). Tezel further teaches culturing the cells onto tissue-culture plastic pre-coated with bovine corneal endothelial extracellular matrix (page 807). Tezel teaches, "The presence or absence of serum-derived hormones, cytokines, carrier proteins, cell attachment factors and cell spreading factors can have a profound effect on the behavior of RPE cells in tissue culture and may mask the specific effects of a particular exogenous cytokine(s) on RPE. For these reasons, several researchers have cultured RPE with reduced or not serum supplementation (page 807)." Tezel further teaches, "This is particularly important for RPE, because RPE cells exhibit phenotypic heterogeneity (page 812)."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Reichel taken with Williams and Funk in

further view of Tezel to culture genetically modified retinal pigment epithelial cells in serum-free medium and in the presence of a feeder layer. One of ordinary skill in the art would have been motivated to culture the RPE cells in the presence of a feeder layer because Williams teaches that culturing stem cells in the presence of a feeder layer maintains stem-cell phenotype *in vitro* and Funk teaches that RPE cells are progenitor cells. In addition, one of ordinary skill in the art would have been motivated to use serum-free medium in the method because Tezel teaches that culturing RPE cells in serum free medium avoids the effect of hormone, cytokines, carrier proteins, cell attachment factors and cell spreading factors on the behavior of RPE cells in tissue culture.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/10/05 have been fully considered but they are not persuasive for the reason set forth under the prior 103(a) rejection.

Response to Arguments

Applicant's arguments, see pages 6 and 7 of applicant's argument, filed 2/10/05, with respect to 102(e) as being anticipated by Kovesdi have been fully considered and are persuasive. The rejection of claims 1-6, 9, and 21-24 has been withdrawn because of the amendment to the claims to recite an adenoviral vector comprising no adenoviral coding DNA sequences.

Applicant's arguments, see pages 7 and 8 of applicant's argument, filed 2/10/05, with respect to 102(b) as being anticipated by Baffi have been fully considered and are persuasive.

The rejection of claims 1, 2, 4-6, 9, and 21-24 has been withdrawn because of the amendment to the claims to recite an adenoviral vector comprising no adenoviral coding DNA sequences.

Applicant's arguments, see page 8 of applicant's argument, filed 2/10/05, with respect to 102(b) as being anticipated by Reichel have been fully considered and are persuasive. The rejection of claims 1, 2, 4-6, 9, and 21-24 has been withdrawn because of the amendment to the claims to recite an adenoviral vector comprising no adenoviral coding DNA sequences.

Applicant's arguments, see pages 9 and 10 of applicant's argument, filed 2/10/05, with respect to 103(a) as being unpatentable over Kovesdi in combination with either Tezel or Funk and Williams have been fully considered and are persuasive. The rejection of claims 1, 10, and 25 has been withdrawn because of the amendment to the claims to recite an adenoviral vector comprising no adenoviral coding DNA sequences.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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